PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	25.08.2004
Applicant's or agent's file reference: 032030woMe/sto	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/09437	26.08.2003	28.08.2002

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
EVOTEC NEUROSCIENCES GMBH et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28.12.2004

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,2,6 (all in part); 4,5,7-9,13 (all in full)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 1,2,6 (all in part); 5,13 (all in full) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 4,7-9 (all in full)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3,10-12
Inventive step (IS)	Claims	1,2,6
Industrial applicability (IA)	Claims	

2. Citations and explanations

   see separate sheet

III. Non-establishment of opinion (Continuation)

2. SUPPORT (ART. 6 PCT)

Article 6 PCT requires that the matter for which protection is sought be defined in the claims in a clear and concise manner and that the claims be supported by the description. A claim is considered not to be supported in the sense of Article 6 PCT if the description does not disclose sufficient technical information to allow a person skilled in the art, using his common general knowledge, to carry out the invention within the whole area that is claimed, without undue burden and without using inventive skills. It should be noted that such lack of technical support can also be objected under Art. 5 PCT, the objection being that the disclosure is insufficient to enable the skilled person to carry out the "invention" over the whole area claimed. The requirements of Articles 5 and 6 PCT are both designed to reflect the principle that the terms of a claim should be commensurate with, or be justified by the disclosure of the invention.

The underlying application describes the identification of the differential expression of foap-13 in post-mortem brain tissue derived from AD patients compared to non-AD control individuals. An up-regulation of foap-13 gene transcription in the temporal cortex compared to the frontal cortex of Alzheimer patients was detected which was not detectable in non-AD individuals (p. 22, second §).
The analysis of the differential expression of foap-13 is limited to post-mortem brain tissue collected from AD and non-AD individuals. No experimental data are given demonstrating any differential expression of foap-13 protein.

Claims 1 and 6 relating to *any* neurodegenerative disease are not considered to be supported in the sense of Article 6 PCT due to the following: The molecular mechanisms underlying different neurodegenerative diseases can be of quite different nature. A molecular mechanism only observed for AD can therefore not credibly be extrapolated to any other neurodegenerative disease. Such teaching would not be accepted by the skilled person as an enabling teaching but just as a mere speculation.

Claim 2 refers to the method according to claim 1 wherein the neurodegenerative disease is AD. However, claim 2 as well is not considered to be supported in the sense of Art. 6 PCT due to the following reasons:
Firstly, there is no technical teaching disclosed in the description supporting a method for prognosticating or determining whether a subject is at increased risk of developing Alzheimer's disease, comprising determining a level and/or an activity of a foap-13

gene transcription/ translation product. The description only discloses the differential expression of foap-13 transcripts in post-mortem brain tissue of patients which were already suffering from Alzheimer's disease.
Secondly, there is no technical teaching in the description nor the drawings which could provide credible support for the differential expression of foap-13 translation products. Due to the fact that the differential expression of the transcription product of a gene does not necessarily lead to a differential expression of the translation product, the observed differential expression of foap-13 transcription products cannot provide support for diagnostic methods comprising the detection of the differential expression of foap-13 translation products.
Thirdly, the diagnosis of AD by determining a level and/or activity of a transcription product of the foap-13 gene in any sample of a subject is as well not considered to be supported due to the fact that the differential expression of foap-13 mRNA was only demonstrated in specific brain tissue samples, namely by determining the expression of foap- 13 in a sample from the frontal cortex and in a sample from the temporal cortex.

From what is said above, it follows that the subject matter of claim 13, namely the use of an antibody specifically immunoreactive with a translation product of a gene coding for a foap-13 protein for detecting the pathological state of a cell in a sample from a subject, as well cannot be regarded as being supported as required by Article 6 PCT.

Claim 5 relates to a recombinant non-human animal comprising a non-native foap-13 gene sequence wherein said non-human animal exhibit a predisposition to developing symptoms of neurodegenerative diseases or related disorders. In regard to the technical contribution disclosed in the underlying application the IPEA is of the opinion that such recombinant non-human animal is not supported as required by Article 6 PCT.

An opinion in regard to novelty and inventive step will therefore only be given for those parts of claims 1 , 2 and 6 which are considered to be supported by the description, namely methods for the diagnosis of AD in post-mortem brain tissue samples comprising determining a differential expression of the foap-13 gene in AD brain tissue compared to non AD tissue wherein an up-regulation of foap-13 mRNA in temporal cortex compared to frontal cortex is indicating AD and an assay for screening for a modulator of AD comprising the testing of the level of a transcription product of a gene coding for foap-13.

The lack of support for claims 5 and 13 is such, that no meaningful opinion can be

formed.

V. Reasoned statement (Continuation)

1. CITATIONS

Reference is made to the following documents:

D1: WO0153312 (2001-07-26) & DATABASE GENESEQ [Online] EBI; HUMAN POLYPEPTIDE SEQ. ID NO. 1861 22 October 2001 (2001-10-22), XP002269445 Database accession no. AAM38716

D2: WO0112662 (2001-02-22) & DATABASE GENESEQ [Online] EBI; LAL ET AL.: "Human membrane associated protein MEMAP-12" XP002270793 Database accession no. AAB74706

D3: [Online] HYPOTHETICAL PROTEIN, FOAP-13 retrieved from SWALL Database accession no. Q9NSS4 (database entry annexed to this communication; foap-13 protein sequence also disclosed in XP002247127 retrieved from EMBL Database, accession no. AB028927)

D4: EP-A-1 188 839 (EVOTEC NEUROSCIENCES GMBH) 20 March 2002 (2002-03-20)

2. NOVELTY (Art. 33(2) PCT)

2.1 The technical content/features of the kit claimed in claim 3, e.g. antibodies specific to foap-13 or nucleic acids for detecting foap-13 expression, are considered to be already disclosed in D1 and D2 (see below). The only contribution seen by the IPEA in regard to D1 and D2 are the instructions of how to use the technically effective content/features of the kit. The instructions are used for the mere presentation of information and are therefore not considered to represent a technical feature of the kit. Due to the fact that an invention has to be defined by its technical features (Rule 6.3 PCT) such non-technical feature can neither serve to distinguish an invention from the prior art, i.e. they cannot contribute to novelty of an invention in the sense of Art. 33(2) PCT, nor can they contribute to an inventive step of an invention in the sense of Art. 33(3) PCT.

2.2 D1 discloses a protein with Seq. ID 2 (D1: Seq. ID 1861). Seq. ID 2 represents the protein sequence of the foap-13 protein. D1 as well refers to antibodies specifically reacting with such protein (p. 39, l. 1-6) and nucleic acids for the detection of expression patterns (p. 38 l. 18-35 and Seq.ID 3647).

In the light of D1, the subject matter of claims 3,10-12 is not novel.

2.2.3 D2 discloses the MEMAP-12 protein as well as the cDNA coding for MEMAP-12. The sequence of the MEMAP-12 protein is identical to Seq. ID 2. Polynucleotides encoding MEMAP are used to detect and quantify gene expression in biopsied tissues in which expression of MEMAP is correlated with disease (p. 49, l. 31-p. 50, l. 19). The MEMAP cDNAs are used for the generation of a cDNA expression array (p. 65, l. 23-33, p. 66, l. 15-p. 68, l. 10). The production and diagnostic use of MEMAP specific antibodies is disclosed (p. 71, l. 7-21 and p. 49, l. 13-21).

In the light of D2, the subject matter of claims 3,10-12 is not novel.

2.2.4 D3 discloses a protein with Seq. ID 2.

In the light of D3, the subject matter of claims 10 and 11 is not novel.

3. Inventive step (Art. 33(3) PCT)

3.1 D4 is considered closest prior art for those parts of claims 1, 2 and 6 considered to be supported. D4 discloses the use of flotillin mRNA expression as a marker for AD. The flotillin mRNA is differentially expressed in post-mortem brain tissue of AD- patients compared to non-AD individuals wherein the up-regulation of flotillin mRNA in temporal cortex compared to frontal cortex of AD patients is indicating AD. A method for screening for a modulator of AD comprising testing the level of a transcription product of a gene coding for flotillin is disclosed as well.

The difference between the methods disclosed in D4 and the methods claimed in claims 1, 2 and 6 is that the foap-13 mRNA expression is used as a marker for AD instead of the flotillin mRNA expression.

Due to the fact that the use of foap-13 mRNA expression as a marker for AD appear not to show any effects going beyond those described in regard to the use

of flotillin mRNA expression as a marker for AD, the problem of the underlying application must be seen in the provision of methods as disclosed in D4 using an alternative mRNA which, like flotillin mRNA is differentially expressed in specific post-mortem brain tissue samples, i.e. in the temporal cortex compared to frontal cortex of AD patients compared to non-AD individuals for use as a marker for AD.

The solution is the use of the foap-13 mRNA expression as a marker.

A person skilled in the art trying to solve the problem posed would try to identify further mRNAs being differentially expressed in specific post-mortem brain tissue samples, i.e. in the temporal cortex compared to the frontal cortex of AD-patients compared to non-AD individuals, for use as an alternative marker for AD. Due to the fact that a person skilled in the art is aware that differences in the mRNA expression observed in different tissues under different physiological conditions encompass many different mRNAs and due to the fact that the identification of mRNAs differentially expressed in the temporal cortex compared to frontal cortex in AD and non-AD individuals is already described in D4, a person skilled in the art would have tried with a reasonable expectation of success to identify further such differentially expressed mRNAs without using inventive skills in order to solve the problem posed. The identification/provision of differentially expressed foap-13 mRNA and the use of the foap-13 mRNA expression as a marker for AD is therefore considered not to involve an inventive step because the identification of foap-13 mRNA being differentially expressed is just one of several mRNAs the person skilled in the art would have expected to identify as being differentially expressed as flotillin mRNA.

Therefore, insofar as having been examined, the subject matter of claims 1,2 and 6 is not considered to involve an inventive step.